MAIL STOP APPEAL BRIEF-PATENTS
Attorney Docket No.: 26230

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

DIETRICH, et al.	Confirmation No. 1681
Serial No.: 10/505,138	Group Art Unit: 1618
Filed: August 19, 2004	Examiner: SILVERMAN, E.

For: **ORAL DOSAGE FORM CONTAINING A PDE 4 INHIBITOR AS AN ACTIVE INGREDIENT AND POLYVINYLPYRROLIDON AS EXCIPIENT**

REPLY BRIEF

This is in response to the Examiner's Answer mailed June 2, 2009. Pursuant to 37 C.F.R. §1.193(b)(1), a Reply Brief may be filed within two (2) months of the date of the Examiner's Answer. Accordingly, this Reply Brief is due August 3, 2009, August 2 being a Sunday, and thus this reply is timely filed.

1. Status of Claims

Claims 38-39, 41-48, 53-54, 65, 68-79, and 81-87 are pending and appealed.

2. Grounds of Rejection to be Reviewed on Appeal

A. Rejection of claims 68 and 82-84 under 35 U.S.C. § 112, first paragraph

Whether the identified claims are unpatentable under 35 U.S.C. § 112, first paragraph, as complying with the written description requirement. The Examiner asserts that the phrase "weight average molecular weight" of polyvinylpyrrolidone is allegedly not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the pending claims. The Examiner asserts that since this phrase is allegedly not recited in the specification, and there is no discussion of what type of molecular weight is referred to in the specification, then adding this phrase constitutes new matter.

B. Rejection of claims 38-39, 41, 45-48, 65, 69, 71-79, 81 and 87 under 35 U.S.C. § 103(a)

Whether the identified claims are unpatentable under 35 U.S.C. § 103(a) as obvious over US Published Application No. 20030018071, to Rennard, et al. ("Rennard") in combination with US Patent No. 6,677,362 to Ghebre-Sellassie et al. ("Ghebre-Sellassie") and Remington: The Science and Practice of Pharmacy, 1995 ("Remington").

The Examiner asserts that the primary Rennard et al. reference teaches the combination of certain PDE4 inhibitors with a pharmaceutical carrier. The Examiner admits that the Rennard reference does not teach a process for producing a dosage form using PVP in any amount. The secondary Ghebre-Sellassie reference is applied by the Examiner for teaching a method for preparing a drug-PVP dosage form. See Example I, and claim 1. The Examiner asserts that the Remington reference discusses the use of PVP as a binder for the preparation of dosage forms by

using either aqueous or alcoholic solutions. Page 1618, bottom of column 1. The Remington reference also generally discusses methods of producing dosage forms, including a "new method for granulating" called fluid-bed granulation. Page 1625, top of column 2.

The Examiner asserts that it would have been prima facie obvious to a person of ordinary skill in the art to use PVP in conjunction with the disclosure of Rennard, to granulate the PVP in a fluid bed granulator before mixing with an additional excipient, such as magnesium stearate, and tableting the product. PVP is allegedly obvious to use because Ghebre-Sellassie teaches certain advantages of using PVP, such as increasing the bioavailability of poorly soluble drugs. Accordingly, the Examiner concludes it would have been obvious to use a wet granulation process because this is a typical process for formulating PVP containing articles, and because of the advantages described for fluidized bed granulation. The Examiner asserts that because these manipulations are described or suggested by the art, the artisan would enjoy a reasonable expectation of success.

C. Rejection of claims 68 and 82-84 under 35 U.S.C. § 103(a)

Whether the identified claims are unpatentable under 35 U.S.C. § 103(a) as obvious over US Published Application No. 20030018071, to Rennard, et al. ("Rennard") in combination with US Patent No. 6,677,362 to Ghebre-Sellassie et al. ("Ghebre-Sellassie"), Remington: The Science and Practice of Pharmacy, 1995 ("Remington"), as applied to claims 38-39, 41, 45-48, 65, 69, 71-79, 81 and 87 as described above, and further in view of US Patent No. 5,262,171, to Login et al ("Login").

In addition to Rennard, Ghebre-Sellassie, and Remington, the Examiner relies on Login for its alleged teaching of specific molecular weights of PVP for use in tablets. Notably, the

Examiner previously stated on the record that "Login teaches that PVP suitable for use in tablets has is graded as K-30 to K-120 molecular weight. The artisan understands that this corresponds to molecular weights of approximately 9,700 Daltons to 3,470,000 Daltons (see PVP product disclosure, cited on PTO 892)." Page 7 of the Official Action dated February 27, 2008.

The Examiner asserts that it would have been prima facie obvious to a person of ordinary skill in the art to find the optimal molecular weight of PVP within the range taught by Login. Further, the Examiner alleges that the art shows that use of PVP within the useful range will give a predictable result; finding the optimal or working molecular weight of PVP will increase the bioavailability of the drug.

D. Rejection of claims 42-44, 53-54, and 85-86 under 35 U.S.C. § 103(a)

Whether the identified claims are unpatentable under 35 U.S.C. § 103(a) as obvious over US Published Application No. 20030018071, to Rennard, et al. ("Rennard") in combination with US Patent No. 6,677,362 to Ghebre-Sellassie et al. ("Ghebre-Sellassie"), and Remington: The Science and Practice of Pharmacy, 1995 ("Remington"), as applied to claims 38-39, 41, 45-48, 65, 69, 71-79, 81 and 87 as described above, and further in view of Chiou et al., "Pharmaceutical Applications of Solid Dispersion Systems", J. Pharm Sci. 60:1281-1302 (1971) ("Chiou"). In addition to Rennard, Ghebre-Sellassie, and Remington, the Examiner relies on Chiou for its alleged teaching of the use of solid dispersions of drug with PVP to increase the availability of poorly water soluble drugs (pp. 1281-1283).

The Examiner notes that the "Applicants continue by pointing to the Chiou teaching and allege that it teaches away from the instant claims because it teaches that PVP dispersions should be prepared by a solvent method, and that PVP is soluble in a variety of organic solvents." The

Examiner asserts that the Appellants have failed to recognize that PVP is also well known to be water soluble. As such, the Examiner asserts that "the artisan looking to Chiou's suggestion of using a solvent in which PVP is soluble, and knowing that PVP is soluble in water, would clearly find it obvious to use water as the granulating liquid." Accordingly, the Examiner asserts that it would have been prima facie obvious to a person of ordinary skill in the art to use a solid dispersion of the drug and PVP, as suggested by Chiou. For these reasons the Examiner concludes that the artisan would enjoy a reasonable expectation of success because Chiou teaches how to make these types of compositions.

E. Rejection of claim 68, 70, and 82-84 under 35 U.S.C. § 103(a)

Whether the identified claims are unpatentable under 35 U.S.C. § 103(a) as obvious over US Published Application No. 20030018071, to Rennard, et al. ("Rennard") in combination with US Patent No. 6,677,362 to Ghebre-Sellassie et al. ("Ghebre-Sellassie"), Remington: The Science and Practice of Pharmacy, 1995 ("Remington"), as applied to claims 38-39, 41, 45-48, 65, 69, 71-79, 81 and 87 as described above, and further in view of Hatzelmann, et al., "Anti-inflammatory and Immunomodulatory Potential of the Novel PDE4 Inhibitor Roflumilast in Vitro", J. Pharm. Exp. Ther., 297:267-279, (2000) ("Hatzelmann").

The Examiner relies on Hatzelmann for its alleged teaching of an N-oxide of the pyridine of the compound (corresponding to the N-oxide of roflumilast), and that both are useful as pharmaceutical agents and as PDE 4 inhibitors (abstract, materials and methods sections).

The Examiner asserts that it would have been prima facie obvious to a person of ordinary skill in the art to use Hatzelmann's N-oxide of roflumilast in the pharmaceutical dosage form suggested by the combination of cited references. Obviousness allegedly stems from both

roflumilast and its N-oxide being recognized as pharmaceuticals useful for the same purpose. As such, the artisan would allegedly enjoy a reasonable expectation of success.

3. Argument

A. Rejection of claims 68 and 82-84 under 35 U.S.C. § 112, first paragraph

The Examiner has maintained the rejection of claims 68 and 82-84 under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement regarding use of the phrase "weight average molecular weight."

As the basis of this rejection, the Examiner stated the following in the Examiner's Answer, in relevant part:

> The claims specify the "weight average molecular weight" of polyvinylpyrrolidone. As shown by the Odian reference, there are at least three different molecular weight averages of polymers: number average, weight average, and viscosity average. Notably, in any particular polymer sample each of these three types of molecular weights has a different value. The original disclosure does not mention the term "weight average molecular weight" nor is there any discussion in the original disclosure of what type of average molecular weight average is being referred to. The introduction of this new limitation, not originally disclosed or even discussed, constitutes new matter.
>
> ...
>
> Appellants first argue that the artisan would understand the meaning of "weight average molecular weight" and would understand it to be adequately disclosed. This argument is a straw-man. The issue is not whether the meaning of "weight average molecular weight" is known and disclosed; the issue is whether the original disclosure discloses that the average molecular weights of PVP listed therein are weight average molecular weights.
>
> Appellants can only point to one portion of the original disclosure that allegedly supports the notion that the molecular weights referred to in are weight average molecular weights. Appellants rely on page 7 of the specification which discusses various Kollidon polymers. The different Kollidons have alpha numeric codes associated with them, such as Kollidon 12 PF, Kollidon 25, and Kollidon 90 F. Appellants continue that, the PVP manufacturer's information sheet gives the weight average molecular weight for PVP having various "K values," each K value being known in the art to correspond to a weight average molecular weight. Appellants conclude that from this the artisan would recognize that the molecular weights referred in the specification are weight average molecular weights.

> Appellants' argument is flawed. The molecular weights associated with the Kollidons in the specification do not match up with the weight average molecular weights for PVP having corresponding K values. For example, the specification, discloses that Kollidon 30 has a molecular weight of 44,000-54,000 daltons, whereas PVP with a K value of 30 has a weight average molecular weight of 66,800 daltons. Because the alpha numeric codes of Kollidon do not match to the K values, the fact that the artisan understands the meaning of K values (a term of art) does not have any bearing on the artisans understanding of the alpha numeric codes associated with Kollidons. Furthermore, Kollidon is a trademark. It is well established that a trademark specifies the source of goods, but not the nature of the goods. Because Kollidon, whatever its alpha numeric code, does not specify the nature of a material, it cannot provide support for the concept that the molecular weights referred to throughout the specification are weight average molecular weight.

Appellants again respectfully traverse the rejection and incorporate herein by reference in its entirety all arguments presented in the Appeal Brief regarding the patentability of the rejected claims. In addition, Appellants provide the following reply showing how and why the Examiner's assertions are in error.

Appellants point to Beuhler, V., "Kollidon® Polyvinylpyrrolidone for the pharmaceutical industry," pages 1-287 (May 1995) ("Beuhler") that was previously made of record in the present application in an information disclosure statement filed on January 20, 2006. Beuhler is a 287 page technical specification published by manufacturer BASF AG for Kollidon® PVP expressly manufactured for, and made commercially available to, the pharmaceutical industry. Appellants attach a convenience copy of pages 1-2, 5-6, 24, and 34-39 which describes how K Values and MW are determined and defined for commercially available polyvinylpyrrolidones encompassed by the trade name Kollidon®.

Beuhler, at page 34 and Table 16, states that the "average molecular weight of a polymer can be viewed and measured in three different ways": "Weight-average" MW, "Number-

average" MW, and "Viscosity-average" MW. Moreover, Beuhler provides comparative molecular weights of Kollidon® PVP for each of the three types of described molecular weights. Table 17 shows examples of Weight-average MW and Number-average MW for Kollidon® PVP. Table 18 shows examples of Viscosity-average MW for Kollidon® PVP. Odian, the reference relied upon by the Examiner, provides no discussion of PVP and moreover provides no comparative molecular weights of Kollidon® PVP for each of the three types of described molecular weights.

Appellants point out the errors in the Examiner's Answer as follows. The Examiner states:

> Appellants' argument is flawed. The molecular weights associated with the Kollidons in the specification do not match up with the weight average molecular weights for PVP having corresponding K values. For example, the specification, discloses that Kollidon 30 has a molecular weight of 44,000-54,000 daltons, whereas PVP with a K value of 30 has a weight average molecular weight of 66,800 daltons.

Appellants point out that **Beuhler at page 36, Tables 17 & 18, expressly states that Kollidon 30 has a "weight-average" molecular weight of 44,000-54,000; Kollidon 30 has a "number-average" molecular weight of 12,000**; and **Kollidon 30 has a "viscosity-average" molecular weight of 42,500. Moreover, the molecular weight ranges disclosed in Appellants' specification at page 7 for Kollidon 12PF, Kollidon 17PF, Kollidon 25, Kollidon 30, and Kollidon 90F are each exactly the same weight-average molecular weight ranges described in Table 17 of Beuhler.** Accordingly, one of ordinary skill in the art reading Appellants' specification and Beuhler (the manufacturer's specification for Kollidon® PVP) would understand that the Kollidon PVP molecular weights described in the Appellants' specification are the accurate weight-average molecular weights for the specific Kollidons.

The Examiner also states:

> Because the alpha numeric codes of Kollidon do not match to the K values, the fact that the artisan understands the meaning of K values (a term of art) does not have any bearing on the artisans understanding of the alpha numeric codes associated with Kollidons.

Contrary to the Examiner's unsupported assertion, Beuhler at page 24, Table 9, expressly states that specific Kollidon alphanumeric codes (Kollidon grades) correspond to specific known ranges of K-values. For example, Table 9 indicates that Kollidon 30 has a K-value ranging from 27.0-32.4. Accordingly, one of ordinary skill in the art reading the specification in combination with Buehler (the manufacturer's specification for Kollidon® PVP) would understand that Kollidon alphanumeric values disclosed in the Appellants' specification correspond to specific ranges of K-values known in the art at the time of filing.

The Examiner then concludes:

> Furthermore, Kollidon is a trademark. It is well established that a trademark specifies the source of goods, but not the nature of the goods. Because Kollidon, whatever its alpha numeric code, does not specify the nature of a material, it cannot provide support for the concept that the molecular weights referred to throughout the specification are weight average molecular weight.

While it is true that a trademark specifies the source of goods, **there are many examples of trademarked products which have very well-defined structural features which are well known in the art.** While recitation of trademark names are generally not acceptable in patent claims, it is common practice to include alternative descriptions of the trademarked product in the claim language. **In the case of Kollidon® PVP, Buehler is an accurate description of the physical nature of the trademarked Kollidon® PVP product which is commercially available and is disclosed in the Appellants' specification.** As discussed herein, Beuhler provides specific written description and support for the concept that the molecular weights

referred to throughout the specification are weight-average molecular weights. Accordingly, one of ordinary skill in the art reading the specification in combination with Buehler (the manufacturer's specification for Kollidon® PVP) would understand that the Kollidon® trademark as disclosed in the Appellants' specification corresponds to specific ranges of K-values and weight-average molecular weights known in the art at the time of filing. **As evidenced by Beuhler, the specific Kollidon® PVP grades described in the Appellants' specification are standard art-recognized phrases that correspond to art-recognized weight-average molecular weight ranges of the PVP.**

Accordingly, Appellants respectfully request reversal of the Examiner's decision to reject claims 68 and 82-84 under 35 U.S.C. § 112, first paragraph.

B. Rejection of claims 38-39, 41, 45-48, 65, 69, 71-79, 81 and 87 under 35 U.S.C. § 103(a)

The Examiner has maintained the rejection of claims 38-39, 41, 45-48, 65, 69, 71-79, 81 and 87 under 35 U.S.C. § 103(a) over Rennard in combination with Ghebre-Sellassie and Remington.

Appellants again respectfully traverse the rejection and incorporate herein by reference in its entirety all arguments presented in the Appeal Brief regarding the patentability of the rejected claims. In addition, Appellants provide the following reply showing how and why the Examiner's assertions are in error.

The Combination of References Do Not Teach or Suggest All Claim Limitations

As the basis for maintaining this rejection, and asserting that the combination of reference teach or suggest all claim limitations, the Examiner stated the following in the Examiner's Answer:

> Appellants first argue that specific limitations of the claims are not taught. In this vein, appellants first argue that Rennard does not teach the use of PVP. But the rejection at issue is not Rennard alone. In a rejection over more than one reference, arguments that do not consider all of the references cannot be persuasive. Both Ghebre-Sellassie and Remington teach the use of PVP in granulation processes.
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> Appellants next argue that Ghebre-Sellassie does not disclose granulating with an aqueous solution of PVP. Appellants continue that this reference only teaches "solvent-free" granulation. Contrary to Appellants position, Ghebre-Sellassie teaches granulation on a fluid-bed apparatus. Fluid bed granulation is a wet granulation method, as described in further detail in Remington. That claim 1 in Ghebre-Sellassie may teach solvent-free methods does not negate that the reference also teaches fluid-bed granulation. Even if Ghebre-Sellassie only taught dry granulation (which is not the case) Remington discusses the various advantages of fluid-bed granulation over dry granulation.

The Examiner has not addressed Appellants' specific comments regarding what Ghebre-Sellassie teaches or suggests, and fails to directly address Appellants' arguments of record.

Appellants stress that the claims at issue are process claims, and not composition claims. In this regard, Appellants point out again that the current process claims recite the use of granulating with an aqueous solution of PVP while the **Ghebre-Sellassie method teaches use of only "solvent-free" PVP in the core of the granules**. The Ghebre-Sellassie fluid-bed method does not teach adding PVP to the plasticizer/solubilizer spraying solution. Furthermore, the current claims involve granulating a water-insoluble drug containing mixture with an aqueous solution of PVP to form a PVP-containing dosage form, while the Ghebre-Sellassie method teaches spraying the required plasticizer/solubilizer on a solvent-free complex of PVP and active drug to form granules having a drug-PVP core coated with plasticizer/solubilizer. **Ghebre-Sellassie neither recognizes the need for nor discloses a process for granulating a water-insoluble drug containing mixture with an aqueous solution of PVP to form a PVP-containing dosage form.**

The Examiner also states:

> Appellants also argue that Remington does not disclose a process for producing a dosage form using an aqueous PVP solution. Contrary to this allegation, Appellants specification indicates that Kollidon is used to refer to PVP — well and good, an applicant for Remington specifically notes (on page 1618) that, in granulation processes, PVP is a binder that is used in aqueous solvents. Remington also notes that in a fluid-bed process a solution or solvent is sprayed on the bed of suspended particles, and the rate of addition of binder (in the solution) is controlled. So Remington does suggest the use of a binder in solution in a fluid-bed granulation process, and suggests PVP specifically may be an aqueous solution.

The Examiner fails to provide a reasoned argument or discussion of evidence that one of skill in the art reading the combination of references would look to Remington and design **a**

process for producing a dosage form wherein an aqueous solution of PVP is used in the granulation step of the production of a dosage form of a low solubility drug. The Remington reference only generally discusses the use of PVP as a binder for preparation of dosage forms by using either aqueous or alcoholic solutions. Page 1618, bottom of column 1. The Remington reference also generally discusses methods of producing dosage forms, including a "new method for granulating" called fluid-bed granulation. Page 1625, top of column 2. However, **the Remington reference neither recognizes the need for nor discloses a process for producing a dosage form wherein an aqueous solution of PVP is used in the granulation step of the production of a dosage form of a low solubility drug as presently claimed.** In particular, the Examiner makes no mention of how Remington, in combination with the cited references, teaches or suggests using this **aqueous solution of PVP** for the production of a dosage form of a **low solubility drug**. Again, Appellants stress that the present claims are directed to a **process** for producing a dosage form.

Accordingly, the combination of references cited by the Examiner does not teach or suggest each and every element of the presently pending claims for the reasons of record and as supplemented herein.

There is No Motivation to Combine or Modify the References As Proposed

In response to Appellants arguments that there is no motivation to combine or modify the references as proposed, the Examiner stated:

> Appellants further argue that there is no motivation to modify the references as proposed by the examiner. Essentially, Appellants argue that Ghebre-Sellassie method is a solvent free method of spraying on a PVP/drug mixture, whereas instant method requires granulation with a PVP solution. Appellants allege that

> the use of an aqueous PVP solution would not "absolutely and completely not result in Ghebre-Sellassie's intended composition." Appellants conclude that because no prior art teaches replacing the PVP that is mixed with the drug in Ghebre-Sellassie with aqueous PVP that is sprayed, as taught by Remington, there is no motivation to combine.
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> In response, Appellants seem to misunderstand or misconstrue the Examiners position. Ghebre-Sellassie teaches mixing drug and PVP and then spraying further excipients, such as plasticizer and solubilizer, on this mixture in a fluid-bed granulation process. Remington teaches that, in fluid-bed granulation processes, it is customary to include binders in the spraying solution. One example of such a binder is PVP in an aqueous solution. Thus it would be merely following the customary practice in the art to include PVP as a binder in the spraying solution.
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> Put another way, the difference between the Rennard/Ghebre-Sellassie and the claims is not, as Appellants aver, that the claims require removal of PVP from the core of Ghebre-Sellassie and use of PVP as an aqueous solution in the granulating spray. Removal of PVP from Ghebre-Sellassie's core is not required by the claims, which provide that the drug is "mixed with one or more pharmaceutical excipients" before granulating. The difference between Rennard/Ghebre-Sellassie and the claims is only that the claims require that the granulating liquid in the fluid bed granulator include an aqueous solution of PVP, whereas Ghebre-Sellassie does specifically provide for the inclusion of PVP in the granulating solution. Remington, however, indicates that it is common practice to include binders in wet granulation fluid, that PVP is an appropriate binder, and that PVP is to be used in aqueous of alcoholic solutions. Given Ghebre-Sellassie's preference of PVP as a binder, its selection would have been obvious.

Ghebre-Sellassie seeks to produce a solvent-free PVP-drug core coated in a plasticizer/solubilizer solution. There is no suggestion or motivation to modify Ghebre-Sellassie by replacing the plasticizer/solubilizer solution with an aqueous PVP solution. Neither is there a suggestion or motivation to include PVP in the plasticizer/solubilizer spraying solution.

As argued above, the Remington reference only generally discusses methods of producing dosage forms, including a "new method for granulating" called fluid-bed granulation. Page 1625, top of column 2. However, **the Remington reference neither recognizes the need for nor discloses a process for producing a dosage form wherein an aqueous solution of**

PVP is used in the granulation step of the production of a dosage form of a low solubility drug as presently claimed.

In addition, Appellants submit that **there is no motivation to include PVP in Ghebre-Sellassie's plasticizer/solubilizer spraying solution** as suggested by the Examiner. Ghebre-Sellassie requires the plasticizer/solubilizer spray composition, such as one comprising polyethylene glycol, to obtain the allegedly surprising discovery for dispersion formation, such as the intended PVP-drug core composition. Col. 3, lines 64-67. There is no further motivation to modify the Ghebre-Sellassie method to include PVP with the plasticizer/solubilizer. Only in Appellants' specification can motivation be found for using an aqueous solution of PVP in the granulation step of the production of a dosage form of a low solubility drug as presently claimed.

The Examiner also stated:

> Appellants then argue that there is some unexpected result in compositions prepared by the claimed method. Appellants point to page 11 of the specification, which alleges that the inventive methods produce dosage forms have increased bioavailability. In view of Ghebre-Sellassie's teaching of increased bioavailability, this result is not surprising or unexpected. Furthermore, there is no evidence on record supporting the contention of unexpected results; Appellants merely make the allegation that the results are unexpected without any comparative data for support.

Again, Appellants stress that the present claims are directed to a **process** for producing a dosage form, and Ghebre-Sellassie in combination with the cited references does not teach or suggest the claimed process.

> Appellants' comments about the Chiou reference are not well understood in view of this rejection. Chiou is not relied upon in this rejection, but is relied upon in other rejections for teaching the advantages of solid-dispersions. Appellants point to sections of Chiou alleging that PVP/drug solid dispersions can only be prepared by solvent methods (meaning not by granulation). This teaching is not relevant to this rejection, because the claims at issue here do not require solid dispersions. Nonetheless, Ghebre-Sellassie teaches producing solid dispersions of drug and

> PVP by a granulation method, disclosing in the Abstract that the compositions are solid dispersions. It is not surprising that in the twenty-three years between the publication of Chiou (1971) and filing date of Ghebre-Sellassie (1994), new methods of making solid dispersions, previously thought impossible, have been developed. Indeed, Ghebre-Sellassie, which does not mention a solvent method of forming solid dispersions, is entitled "Solid Drug Pharmaceutical Dispersions."

Appellants submit that discussion of Chiou is relevant to this rejection and these other claims as a teaching away reference because Chiou does involve the selection of a solvent method for using PVP to prepare a granulated product as recited in the claims. Accordingly, Appellants maintain their arguments in regard to Chiou's teachings.

Appellants also point out that Ghebre-Sellassie clearly teaches that the disclosed method of wet granulation includes an appropriate solubilizer/plasticizer in order to achieve "surprising results." **This discovery by Ghebre-Sellassie does not render Chiou "out of date." On the contrary, Chiou remains quite valid in its teachings and puts into perspective the technical contribution Ghebre-Sellassie makes in adding solubilizer/plasticizer to achieve a granulated product.** The Examiner does not point to any other reference in the intervening twenty three years that renders Chiou supposedly "out of date" and merely proposes that the artisan would combine the teachings of Ghebre-Sellassie and Remington and ignore Chiou because it is "out of date." **The validity of a reference does not expire merely because it has not been improved upon or disproven over 23 years. Ghebre-Sellassie "improves" upon Chiou only by adding solubilizer/plasticizer. Appellants' application is the first known instance where it can be shown that Chiou teaches away from the recited subject matter.**

No Reasonable Likelihood of Successfully Modifying the References

In response to Appellants arguments that there is no reasonable likelihood of successfully modifying the references as proposed, the Examiner stated:

> Appellants' last argument is deals with expectation of success. Their argument is that there would be no likelihood to succeed in modifying the Chiou method by the other pieces of prior art. Appellants constantly point to Chiou here, but the Examiner cannot understand why. This rejection does not include the Chiou reference, and so the Examiner has not suggested that the Chiou reference be modified to meet the limitations of these claims. Nonetheless, as discussed above, Chiou's teachings about methods of making solid dispersions must be looked in view of all of the prior art, including Ghebre-Sellassie. The artisan is not an automaton. When Chiou, in 1971, stated that PVP/drug solid dispersions could only be made by a solvent method, but Ghebre-Sellassie in 1994 made PVP/drug solid dispersions by another method, the artisan would understand that Chiou is merely out of date on that point.

As argued above, Appellants point out that Ghebre-Sellassie clearly teaches that the disclosed method of wet granulation includes an appropriate solubilizer/plasticizer in order to achieve "surprising results." **This discovery by Ghebre-Sellassie does not render Chiou "out of date." On the contrary, Chiou remains quite valid in its teachings and puts into perspective the technical contribution Ghebre-Sellassie makes in adding solubilizer/plasticizer to achieve a granulated product.** The Examiner does not point to any other reference in the intervening twenty three years that renders Chiou supposedly "out of date" and merely proposes that the artisan would combine the teachings of Ghebre-Sellassie and Remington and ignore Chiou because it is "out of date." **The validity of a reference does not expire merely because it has not been improved upon or disproven over 23 years. Ghebre-Sellassie improves upon Chiou only by adding solubilizer/plasticizer. Appellants'**

application is the first known instance where it can be shown that Chiou teaches away from the recited subject matter.

The combination of Chiou and Ghebre-Sellassie clearly do not point to using a granulation step with an aqueous PVP solution either in combination with, or in place of, Ghebre-Sellassie's solubilizer/plasticizer to obtain a successful PVP-drug formulation. The combination of references indicates that modifying Ghebre-Selassie by replacing the solubilizer/plasticizer polyethylene glycol with aqueous PVP would not provide a reasonable likelihood of success of obtaining the claimed process. Similarly, the combination of references indicates that modifying Ghebre-Selassie by adding aqueous PVP to the solubilizer/plasticizer polyethylene glycol spraying solution would not provide any reasonable expectation of successfully providing an added structural or functional benefit to Ghebre-Sellassie's solubilizer/plasticizer spraying solution. Accordingly, there is no reasonable likelihood of success of adding aqueous PVP to Ghebre-Sellassie's solubilizer/plasticizer spraying solution to obtain the claimed process.

Therefore, for the reasons of record, and as supplemented herein, Appellants submit that Rennard in combination with Ghebre-Sellassie and Remington does not render Appellants' pending claims obvious. Therefore, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 38-39, 41, 45-48, 65, 69, 71-79, 81 and 87 under 35 USC §103(a).

C. Rejection of claims 68 and 82-84 under 35 U.S.C. § 103(a)

Whether the identified claims are unpatentable under 35 U.S.C. § 103(a) as obvious over US Published Application No. 20030018071, to Rennard, et al. ("Rennard") in combination with US Patent No. 6,677,362 to Ghebre-Sellassie et al. ("Ghebre-Sellassie"), Remington: The Science and Practice of Pharmacy, 1995 ("Remington"), as applied to claims 38-39, 41, 45-48, 65, 69, 71-79, 81 and 87 as described above, and further in view of US Patent No. 5,262,171, to Login et al ("Login"). In addition to Rennard, Ghebre-Sellassie, and Remington, the Examiner relies on Login for its alleged teaching of specific molecular weights of PVP for use in tablets.

Appellants again respectfully traverse the rejection and incorporate herein by reference in its entirety all arguments presented in the Appeal Brief regarding the patentability of the rejected claims.

In light of the arguments presented in the Appeal Brief and as supplemented herein, Appellants submit that Rennard in combination with Ghebre-Sellassie and Remington does not render Appellants' pending claims obvious. Login cannot remedy these deficiencies present in the combination of Rennard, Ghebre-Sellassie, and Remington. Login, in combination with the cited prior art, provides no further teaching or suggestion to show that drug-polyvinylpyrrolidone solid dispersions can be prepared using an aqueous solution of polyvinylpyrrolidone as recited in the present claims. Accordingly, Appellants respectfully request that this rejection be withdrawn.

D. Rejection of claims 42-44, 53-54, and 85-86 under 35 U.S.C. § 103(a)

The Examiner has maintained the rejection of claims 42-44, 53-54, and 85-86 under 35 U.S.C. § 103(a) as obvious over US Published Application No. 20030018071, to Rennard, et al.

("Rennard") in combination with US Patent No. 6,677,362 to Ghebre-Sellassie et al. ("Ghebre-Sellassie"), Remington: The Science and Practice of Pharmacy, 1995 ("Remington"), as applied to claims 38-39, 41, 45-48, 65, 69, 71-79, 81 and 87 as described above, and further in view of Chiou et al., "Pharmaceutical Applications of Solid Dispersion Systems", J. Pharm Sci. 60:1281-1302 (1971) ("Chiou").

Appellants again respectfully traverse the rejection and incorporate herein by reference in its entirety all arguments presented in the Appeal Brief and presented herein above regarding the patentability of the rejected claims. In addition, Appellants provide the following reply showing how and why the Examiner's assertions are in error.

As the basis for maintaining this rejection, and asserting that the combination of references teach or suggest all claim limitations, the Examiner stated the following in the Examiner's Answer:

> Appellants argue that because Chiou teaches that PVP/drug dispersions can only be formed by the solvent method, and Ghebre-Sellassie mixes drug and PVP without solvent (before granulation), the artisan would not be able to make solid dispersions as claimed. Instead, according to Appellant, an artisan desiring solid dispersions would avoid the methods of Ghebre-Sellassie.
>
> In making this argument, Appellants completely ignore that Ghebre-Sellassie teaches solid dispersions of PVP and drug, and does not use the "solvent method" of Chiou to make them. The artisan would not be, troubled by this apparent contradiction. Chiou was published in 1971, Ghebre-Sellassie filed for his patent in 1994. In the twenty-three intervening years, Ghebre-Sellassie recognized that it is possible to do what Chiou thought could not be done: making a PVP/drug dispersion by a method other than the solvent method. The artisan would understand that Chiou is merely somewhat out of date on this point. At the time that the instant application was filed, the artisan would know how to make a PVP/drug dispersion by the means disclosed in Ghebre-Selassie, and would be undeterred by the fact that in 1994 it was possible to do that which, in 1971, was deemed impossible. This is not a case where the prior art indicates that it would not be possible to do what Appellants' have done – this is a case where the prior art teaches how to do exactly what Appellants have done.

As argued above, Appellants point out that Ghebre-Sellassie clearly teaches that the disclosed method of wet granulation includes an appropriate solubilizer/plasticizer in order to achieve "surprising results." This discovery by Ghebre-Sellassie does not render Chiou "out of date." The validity of a reference does not expire merely because it has not been improved upon or disproven over 23 years. On the contrary, **Chiou remains quite valid in its teachings and puts into perspective the technical contribution Ghebre-Sellassie makes in adding solubilizer/plasticizer to achieve a granulated product. Ghebre-Sellassie "improves" upon Chiou by adding solubilizer/plasticizer to the spraying solution to be sprayed upon the solvent-free PVP-drug core.** Further, as argued above, the combination of references provides no suggestion or motivation to include PVP in the Ghebre-Sellassie spraying solution. Moreover, **the Examiner remains silent on the fact that Ghebre-Sellassie can only obtain the drug-PVP formulation by including an appropriate solubilizer/plasticizer in the spraying solution** used during the granulation step.

One of skill in the art reading Chiou and Ghebre-Sellassie in combination with the cited references would understand that **drug-PVP solid dispersions can only be prepared by the solvent method of Chiou or by using the required solubilizer/plasticizer spraying solution on a drug-PVP core described by Ghebre-Sellassie.** One of skill in the art understands that **the "solvent method" described in Chiou does not, and cannot, comprise using an aqueous solution of PVP in the spraying solution** as recited in the present claims. In addition, one of skill in the art would understand that in order to successfully use **Ghebre-Sellassie's method, a solubilizer/plasticizer solution is sprayed upon the drug-PVP core. There is no suggestion or motivation to add PVP to the "surprisingly effective" solubilizer/plasticizer solution.**

Moreover, one of skill in the art would not be motivated to further modify the solubilizer/plasticizer solution because of its "surprisingly effective" properties in forming the drug-PVP formulation. There would be no motivation to further add aqueous PVP, or any other component, to the spraying solution since Ghebre-Sellassie has already achieved effective drug-PVP granulation by using the "surprisingly effective" solubilizer/plasticizer in the spraying of a drug-PVP core. The combination of references neither recognizes the need for nor discloses a process for producing a dosage form wherein an aqueous solution of PVP is used in the granulation step of the production of a dosage form of a low solubility drug as presently claimed.

In light of the arguments presented in Section B above, Appellants submit that Rennard in combination with Ghebre-Sellassie and Remington does not render Appellants' pending claims obvious. Chiou cannot remedy these deficiencies present in the combination of Rennard, Ghebre-Sellassie, and Remington. Accordingly, Appellants respectfully request that this rejection be withdrawn.

E. Rejection of claims 68, 70, and 82-84 under 35 U.S.C. § 103(a)

Whether the identified claims are unpatentable under 35 U.S.C. § 103(a) as obvious over US Published Application No. 20030018071, to Rennard, et al. ("Rennard") in combination with US Patent No. 6,677,362 to Ghebre-Sellassie et al. ("Ghebre-Sellassie"), Remington: The Science and Practice of Pharmacy, 1995 ("Remington"), as applied to claims 38-39, 41, 45-48, 65, 69, 71-79, 81 and 87 as described above, and further in view of Hatzelmann et al.,

Hatzelmann, et al., "Anti-inflammatory and Immunomodulatory Potential of the Novel PDE4 Inhibitor Roflumilast in Vitro", J. Pharm. Exp. Ther., 297:267-279, (2000) ("Hatzelmann").

What is alleged to be lacking from the teachings of Rennard, Ghebre-Sellassie, and Remington is a teaching of the N-oxide of roflumilast. The Examiner relies on Hatzelmann for its alleged teaching of an N-oxide of the pyridine of the compound (corresponding to the N-oxide of roflumilast), and that both are useful as pharmaceutical agents and as PDE 4 inhibitors (abstract, materials and methods sections).

In light of the arguments presented in the Appeal Brief and as supplemented herein, Appellants submit that Rennard in combination with Ghebre-Sellassie and Remington does not render Appellants' pending claims obvious. Hatzelmann cannot remedy these deficiencies present in the combination of Rennard, Ghebre-Sellassie, and Remington. Hatzelmann, in combination with the cited prior art, provides no further teaching or suggestion to show that drug-polyvinylpyrrolidone solid dispersions can be prepared using an aqueous solution of polyvinylpyrrolidone as recited in the present claims. Accordingly, Appellants respectfully request that this rejection be withdrawn.

In view of the foregoing, Appellants respectfully request the reversal of the Examiner's rejections and the allowance of the pending claims. If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account No. 14-0112.

Respectfully submitted,

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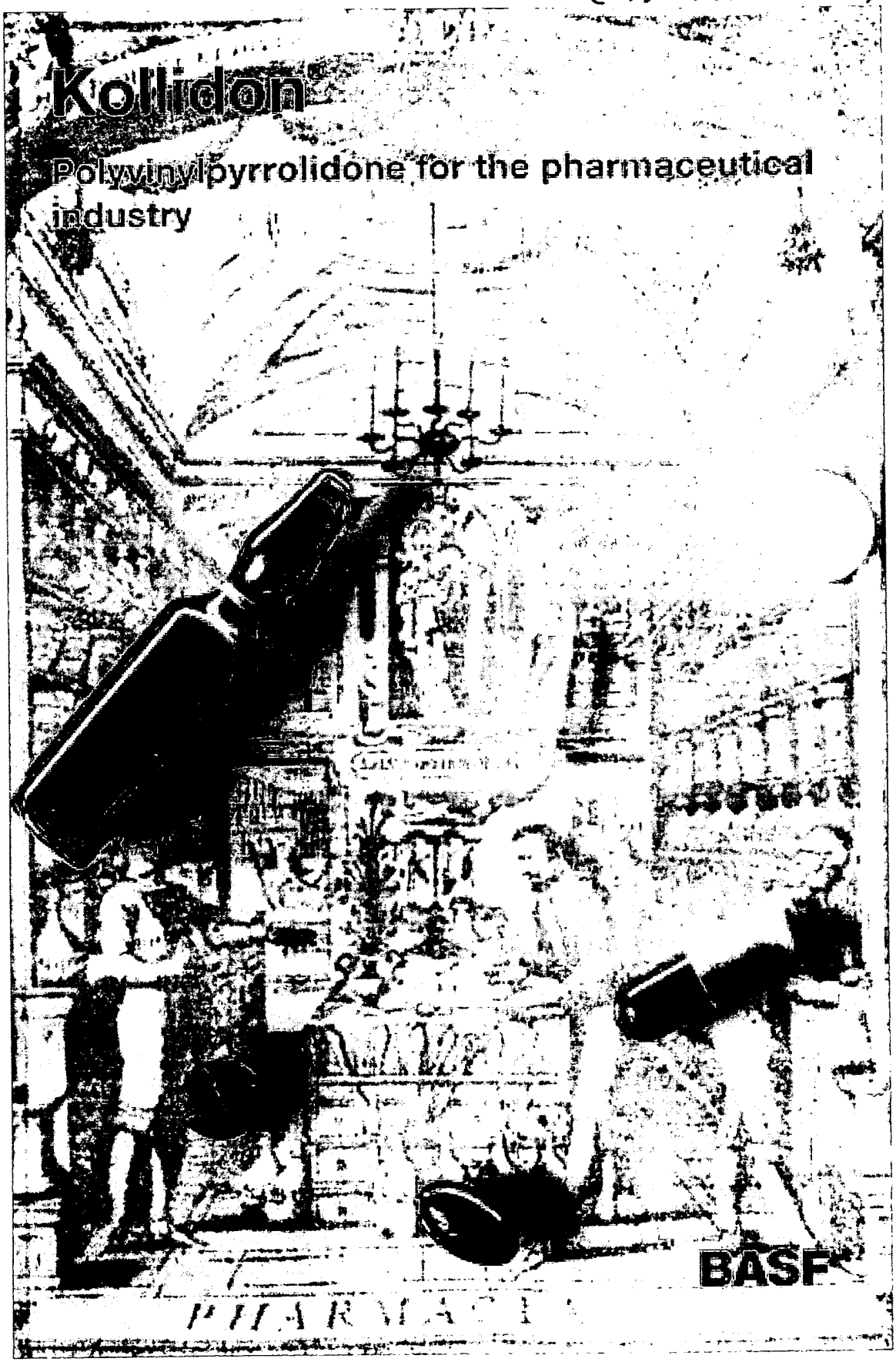

Volker Bühler

Kollidon®

Polyvinylpyrrolidone for the pharmaceutical industry

BASF Aktiengesellschaft
Feinchemie
D-67056 Ludwigshafen

BASF

May 1995
(2nd edition)

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2.2.3.2 K-value

The average molecular weight of the soluble Kollidon grades is expressed in terms of the K-value in the pharmacopoeias valid in Europe and the USA [13]. It is calculated from the relative viscosity in water and always forms a part of the commercial name. The K-values specified in Section 2.2.1.2, which are almost identical with the ranges specified in the European Pharmacopoeia (Ph.Eur.), apply to the soluble Kollidon grades. As can be seen from Table 9, the K-value ranges specified in the USP are slightly wider. The USP and Ph.Eur. specify limits of 85–115% for nominal K-values up to 15, while for nominal K-values above 15, the USP allows limits of 90–108% and the Ph.Eur. 90–107% of the K-value. The values in Table 9 were calculated from the data in Table 7 (formula: see Section 2.3.2.1).

Table 9: Pharmacopoeia specifications for the K-values of povidone (calculated from Table 7)

Nominal K-value	USP specification	Ph.Eur. specification
12	10.2–13.8	10.2–13.8
17	15.3–18.4	15.3–18.2
25	22.5–27.0	22.5–26.8
30	27.0–32.4	27.0–32.1
90	81.0–97.2	81.0–96.3

Figures 8 and 9 show the relative viscosity as a function of the K-value for 1% and 5% solutions in water.

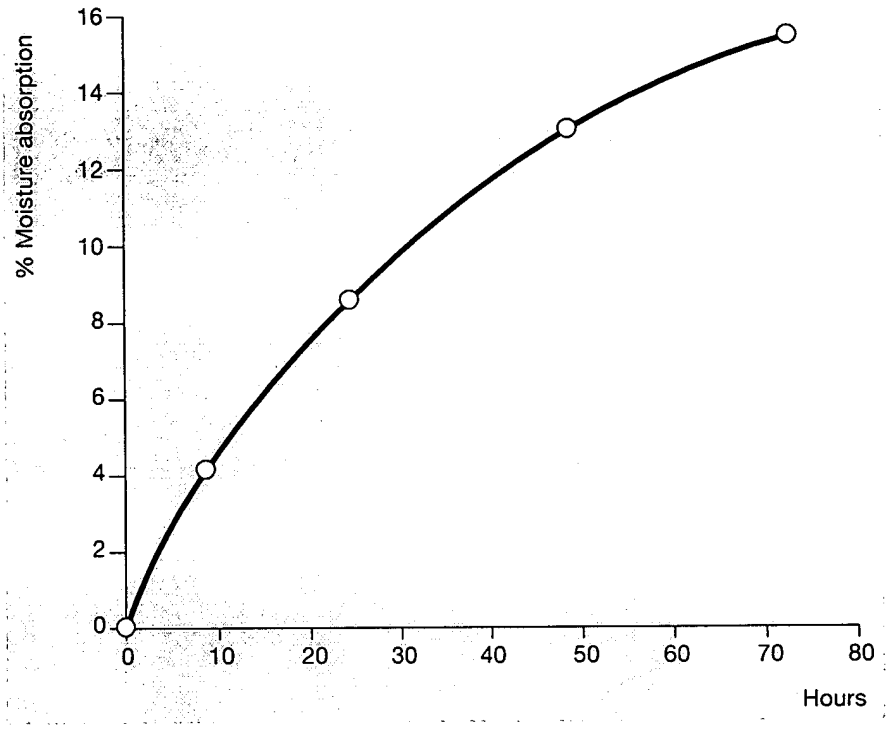

Fig. 14: Moisture absorbed by Kollidon 30 films with 2.5% glycerol over 72 hours at 25 °C and 85% rel. humidity

2.2.6 Molecular weight

2.2.6.1 Average molecular weight

The average molecular weight of a polymer can be viewed and measured in three different ways [14, 212] as indicated in Table 16 below.

Table 16: Average molecular weights of polymers and their methods of determination

Type of average molecular weight	Symbol	Method of determination
Weight-average	$\bar{M}w$	Light scattering, ultracentrifuge
Number-average	$\bar{M}n$	Osmometry, membrane filtration
Viscosity-average	$\bar{M}v$	Viscosity

As these methods of determining the average molecular weight are relatively complicated, it is now expressed in terms of the K-value, in accordance with the European and U.S. Pharmacopoeias (see also Section 2.2.3.2).

Fig. 15 shows the relationship between the K-value and the average molecular weight, determined by light scattering.

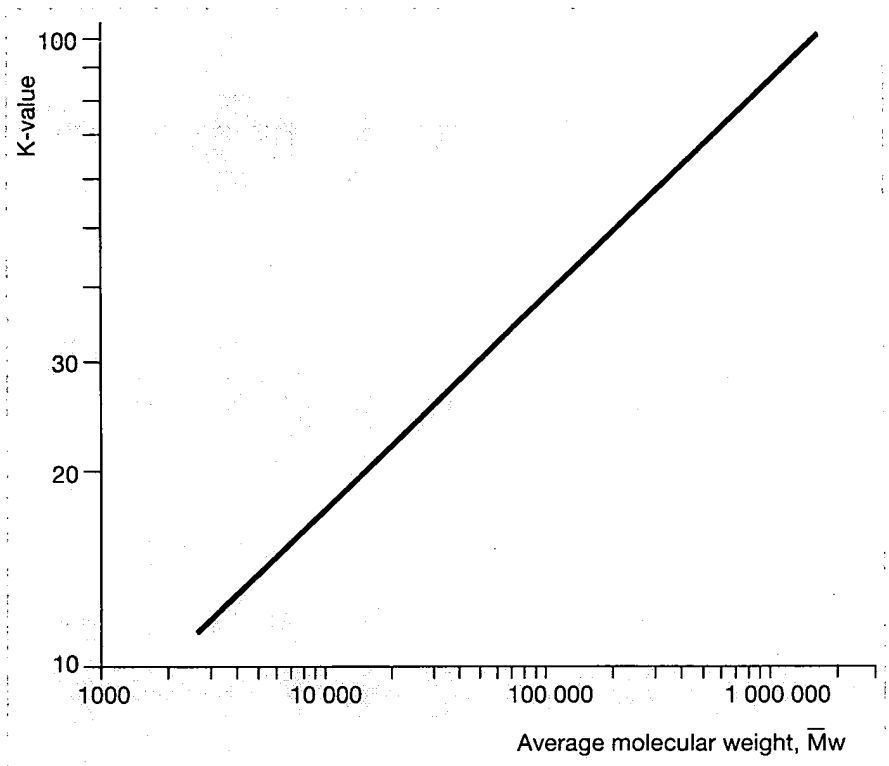

Fig. 15: K-value versus average molecular weight, $\bar{M}w$ determined by light scattering

The *weight-average* of the molecular weight, $\bar{M}w$ is determined by methods that measure the weights of the individual molecules. The measurement of light scattering has been found to be the most suitable method for the Kollidon grades [212]. Values determined by this method are given in Table 17. Recent results do not always agree well with older results, as the apparatus used has been improved significantly over the years. The products themselves have not changed, however.

The *number-average* of the molecular weight, $\bar{M}n$ is determined by methods that measure the number of molecules. This value is very seldom determined or published for the Kollidon grades or for povidone generally. Table 17 shows some older values.

Table 17: Weight and number-averages of the molecular weights of the soluble Kollidon grades

Kollidon grade	Weight-average (recent determinations)	Weight-average (measured before 1975)	Number-average (older determinations)
Kollidon 12 PF	2000 – 3000	2500	1300
Kollidon 17 PF	7000 – 11000	9000	2500
Kollidon 25	28000 – 34000	25000	6000
Kollidon 30	44000 – 54000	40000	12000
Kollidon 90 F	1000000 – 1500000	700000	360000

The *viscosity-average* of the molecular weight, $\bar{M}v$ has attracted greater interest recently, as it can be calculated direct from the relative viscosity, the intrinsic viscosity or the K-value (see Section 2.3.2.2). Table 18 shows typical viscosity-average values for the different Kollidon grades.

Table 18: Viscosity-average values of the molecular weight, $\bar{M}v$ for the soluble Kollidon grades, calculated from the K-value [212]

	$\bar{M}v$ calculated from the nominal K-value	$\bar{M}v$ calculated from the K-value range given in Ph.Eur.
Kollidon 12 PF	3900	2600 – 5500
Kollidon 17 PF	9300	7100 – 11000
Kollidon 25	25700	19300 – 31100
Kollidon 30	42500	31700 – 51400
Kollidon 90 F	1100000	790000 – 1350000

2.2.6.2 Molecular weight distribution

Polymers do not consist only of molecules of the same molecular weight, they consist of molecules with a range of molecular weights with, in the ideal case, a Gaussian distribution.

Gel permeation chromatography:

The molecular weight distribution of the soluble grades of Kollidon can best be determined with the aid of high-performance gel permeation chromatography. Fig. 16 gives a qualitative comparison between Kollidon 17 PF and Kollidon 30 in a gel permeation chromatogram marked at a molecular weight of 35000.

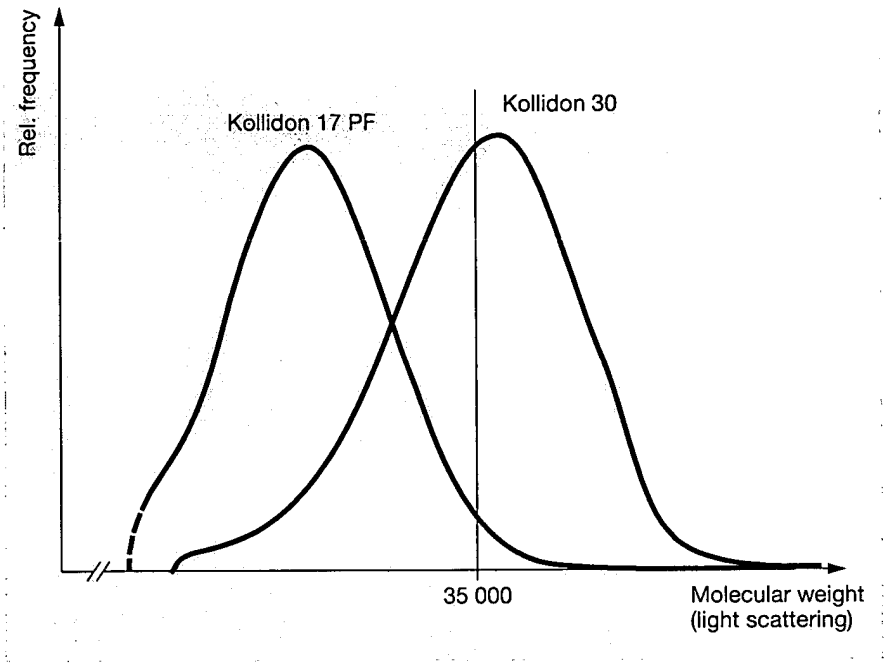

Fig. 16: Qualitative comparison of the molecular weight distributions of Kollidon 17 PF and Kollidon 30. Gel permeation chromatogram marked at a molecular weight of 35000

Fig. 17 shows the integral curve for a gel permeation chromatogram of Kollidon 17 PF, which gives a quantitative evaluation. The chromatograph was calibrated with povidone calibration fractions with sharply defined molecular weight ranges between 20000 and 44000. The curve shows that the cumulative percentage with a molecular weight greater than 35000 is less than 5% for Kollidon 17 PF.

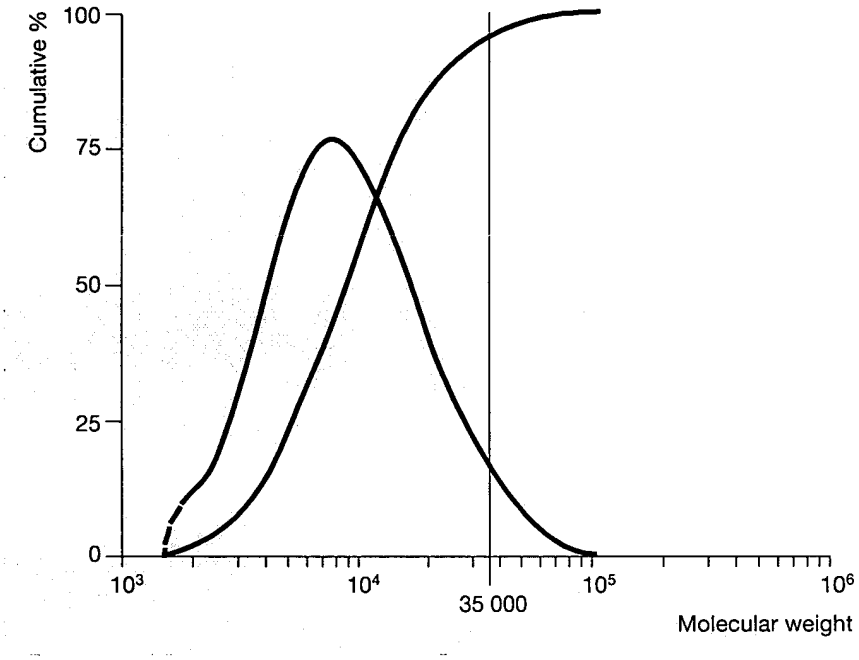

Fig. 17: Molecular weight distribution curve of Kollidon 17 PF with integral curve, determined by GPC

Fractionation:

A further means of obtaining information on the distribution of molecular weights in povidone is fractionation. This technique is very imprecise and gives only the proportions above and below a particular molecular weight. It is based on the difference in solubility of molecules of different sizes in certain solvents and their mixtures, e.g. water and isopropanol or ether.

This fractionation method has been adopted by the former Japanese Pharmacopoeia as a means of characterizing the high and low-molecular components of povidone. Certain combinations of water, isopropanol and acetone have been selected for this purpose and limits that have been established empirically are shown in Table 19 (Method: see Section 2.3.2.3).

Table 19: Limits for the low and high-molecular components of povidone according to Jap.Ph. XII (former monographs)

Kollidon grade	Low-molecular fraction	High-molecular fraction
Kollidon 25	max. 15%	max. 20%
Kollidon 30	max. 15%	max. 20%
Kollidon 90 F	max. 20%	–

Diafiltration:

In special cases, diafiltration with calibrated membranes can also be used to determine the proportions above and below a particular molecular weight. However, extensive testing has shown that the variations in the results are too great for the method to be readily reproducible, because of differences in pore size from one membrane to another and because of changes in the properties of the membranes after repeated use.

Electrophoresis:

Electrophoresis has also been described in the literature as a technique for determining the molecular weight distribution of soluble Kollidon grades [377].

2.2.7 Complexation, chemical reactions

2.2.7.1 Complexation

Because of their chemical structure, the Kollidon grades form chemical complexes with a number of substances, including pharmacologically active substances [7, 8, 44d, 99, 103, 106, 179, 220]. Both the solubility and the stability of these complexes vary greatly. They almost always dissolve more readily or more quickly in water than the pure drug. Detailed information on the increase in solubility for individual active substances is given in Sections 2.4.3 and 2.4.5.

The only known exceptions, i.e. substances that become less soluble or even precipitate, are polyphenols, e.g. tannin, and hexylresorcinol [10, 108]. In general, all complexes with povidone are formed only under acidic conditions and are unstable and can decompose in the alkaline pH range. Typical examples are cobalt [388] and the disinfectant, PVP-iodine [9] in which all the iodine, with the exception of a few ppm of free iodine, is complexed.

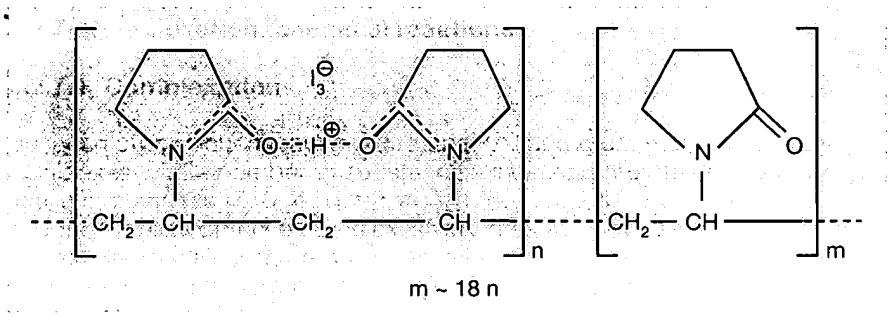

Fig. 18: PVP-iodine complex

In systematic investigations into the dependence of complex formation on structure, no difference was found between soluble polyvinylpyrrolidone (povidone) and insoluble polyvinylpyrrolidone (crospovidone) for complexes with organic compounds [192].